



At the Dawn of a Therapeutic Revolution for Atopic Dermatitis: An Interview with Dr Anne-Claire Fougrousse

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ABSTRACT

Dr Anne-Claire Fougrousse is Head of Dermatology at the Bégin Hospital in Saint-Mandé, France, and scientific coordinator of a French network of dermatologists and allergists (ResoEczema). The focus of her work is to improve the care of adolescent and adult patients with atopic dermatitis (AD), a chronic, pruritic inflammatory skin disease that substantially impacts patient quality of life. In this interview, Dr Fougrousse provides an overview of the clinical presentation of adult patients with AD and describes available treatments. Today, topical agents like emollients and corticosteroids are the mainstay of AD therapy, and patients with lesions that are resistant to optimally administered topical treatment can also receive phototherapy or systemic therapy with ciclosporin. Dr Fougrousse discusses her hopes for the future of AD therapy with the recent development of biologicals like dupilumab, which may provide improvements in clinical outcomes and quality of life for patients with moderate-to-severe AD. In the next few years,

the therapeutic arsenal for AD will likely expand to include more systemic therapies providing sustained symptom control. The real challenge will be to ensure that the maximum number of patients with AD achieve clinical benefits from these new treatments.

Keywords: Atopic dermatitis; Dermatologist; Expert's perspective

Key Summary Points

In this interview, Dr Fougrousse provides an overview of the clinical presentation of adult patients with atopic dermatitis (AD) and describes available treatments.

Since the recent development of biologicals for AD, we are at the dawn of a therapeutic revolution with the emergence of various treatment options with sustained control of the symptoms and enhanced quality of life of patients.

The challenge is to ensure that the maximum number of patients with AD benefit from these medical advances.

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CAN YOU GIVE US A BRIEF DESCRIPTION OF YOUR CAREER TO DATE?

My career began at the University of Aix-Marseille, France, where I received my degree in medicine with specialisation in dermatology in 2010. Subsequently, I worked as a military dermatologist at the Hospital Legouest in Metz, France, from 2011 to 2013, and then at the military Bégin Hospital in Saint-Mandé, France, from 2013 to 2018. Since September 2018, I have been the Head of Dermatology at Bégin Hospital, where I manage the treatment of adolescents and adults with different chronic inflammatory dermatoses, including atopic dermatitis (AD).

CAN YOU TELL US ABOUT YOUR ROLE IN RESOECZEMA?

ResoEczema (<https://www.resoeczema.fr/>) is a French network of 65 specialists in eczema. Created in 2017, ResoEczema is part of the Reso association, a larger network of 600 dermatologists and other specialists (e.g. allergy specialists and surgeons), who see patients with various chronic inflammatory dermatoses, such as AD, psoriasis, urticaria, hidradenitis suppurativa and vitiligo. My role as a Reso coordinator is to manage the logistics, moderation and organisation of the various networks within the association. As a Reso scientific coordinator, I supervise clinical research programs within the different networks, in particular collaborative projects within ResoEczema.

WHAT ARE THE MAIN OBJECTIVES OF RESOECZEMA?

In France, most patients with AD do not have easy access to specialist care, either in private practice or in a hospital dermatology unit. Medications for the treatment of moderate-to-severe AD, whether administered orally or by injection, must be prescribed by hospital practitioners, and many patients only receive appropriate care for their condition in the advanced stages of disease.

The first objective of ResoEczema is to help patients to better understand their disease and its substantial impact on quality of life, and to provide up-to-date information about available treatments and ongoing research. ResoEczema also includes a comprehensive list of dermatologists and allergologists for each region so that patients can easily contact specialists and receive appropriate care.

Another objective is to promote and develop communication exchange among healthcare professionals to improve the follow-up of patients with AD. ResoEczema provides digital tools for sharing information, which, for example, allows an adequate coordination between hospital-based healthcare teams and dermatologists in private practice. Training sessions are also provided to healthcare professionals within the Reso association to update their knowledge and skills.

Finally, ResoEczema aims to develop e-medicine and new communication technologies for the benefit of patients. Consultation modalities have changed profoundly as a result of the COVID-19 pandemic and the associated lockdown measures, which had a clear negative impact on the management of chronic inflammatory dermatoses for both patients and dermatologists [1]. This highlights the value in implementing online dermatology consultations and digital methods in order to help patients cope with their disease and reduce its impact on their daily life.

WHAT IS THE TYPICAL CLINICAL PRESENTATION OF A PATIENT WITH ATOPIC DERMATITIS?

AD is a chronic, pruritic inflammatory skin disease that follows a relapsing course, with a complex pathogenesis involving genetic, immunological and environmental factors that lead to a dysfunctional skin barrier and dysregulation of the immune system [2]. As a result, environmental factors (e.g. bacteria, irritants or allergens) cause the skin of individuals with AD to become red and itchy. Pruritus, a hallmark of the condition, is responsible for much of the disease burden borne by patients, such as altered sleep [3].

There are several different clinical forms of AD and wide variations in symptoms between patients. The most common clinical findings include erythema, oedema, xerosis, erosions/excoriations, oozing, crusting and lichenification, but these vary with patient age and the chronicity of lesions. The extent of lesions is also variable; they can be located on multiple sites, including the face and neck, the creases of the knees and elbows and the hands, or limited to one or two sites, such as dyshidrotic eczema of the hands and feet.

Common comorbidities of AD include other atopic conditions that should be considered in the management of these patients, such as food allergies, asthma and allergic rhinitis/rhinoconjunctivitis [4].

IS THIS A CHILDHOOD DISEASE?

AD is a chronic disease that occurs most frequently in children, but also affects many adults. The onset of AD most commonly occurs between 3 and 6 months of age, with approximately 60% of patients developing an AD eruption in the first year of life and 90% by 5 years of age [5]. While the disease usually resolves by adulthood in the majority of affected individuals, 10–30% of patients have persistent AD; a small percentage of patients first develop symptoms as adults [6]. In France, AD occurs in 10% of children and 4% of adults [7].

These are the patients that I routinely treat in clinical practice.

WHAT IS THE EFFECT OF ATOPIC DERMATITIS ON QUALITY OF LIFE?

AD has a profoundly negative effect on patient quality of life [8], and the greater the severity of the AD, the more quality of life is impaired. AD lesions are associated with persistent pain, and sleep disturbance is common in patients with AD, stemming largely from the significant and constant pruritus (itching) associated with the disease [3]. This is a major factor leading to impaired quality of life. Sleep disturbance and the intensity of itching are considered in some of the scores used to assess the severity of AD. For example, the SCORing Atopic Dermatitis (SCORAD) index incorporates both objective physician estimates of extent and severity as well as subjective patient assessment of itch and sleep loss [9].

The overt nature of the disease has a strong impact on patients' daily activities, including effects on interpersonal relationships and work performance, and affects their psychological state because they feel that other people view them differently. When assessing the severity of AD, it is important to carefully consider the various dimensions that are altered by the disease with the help of scales measuring quality of life, such as the Dermatology Life Quality Index (DLQI) [10].

While sleep disorders and severe pruritus can strongly affect the well-being of patients with AD, associations with neuropsychiatric conditions (depression, anxiety) can occur in the most severe cases [11]. Healthcare professionals must be aware of and assess these conditions, and should discuss with the patient how best to manage them as part of the treatment plan.

IN GENERAL, WHAT IS THE PATIENT PATHWAY?

Topical agents are the mainstay of AD therapy. The application of moisturisers soon after bathing to improve skin hydration is an integral

part of treatment as their use can reduce disease severity and the need for pharmacological intervention [12]. The addition of oils, emollients and other additives to bath water can also help. Moisturisers can be the main primary treatment for mild AD and should be part of the regimen for moderate-to-severe disease.

Topical corticosteroids and topical calcineurin inhibitors are two classes of anti-inflammatory therapy that are used to treat patients with mild-to-moderate AD [12]. AD is characterised by flares, alternating with periods of relative quiescence after anti-inflammatory therapy. The strategy required to minimise recurrent flares varies depending on the individual and the frequency, severity and sites of disease. Daily moisturiser use can lengthen the time before the first flare, and anti-inflammatory therapy will only be reinitiated when new lesions appear. This is considered a reactive approach to long-term AD management. However, individuals who experience frequent, repeated flares at the same body sites can benefit from a more proactive approach, whereby topical corticosteroids or topical calcineurin inhibitors are applied once or twice weekly to both previously and newly involved skin [13].

Phototherapy is recommended as treatment for both acute and chronic AD in patients who cannot achieve clinical improvement and disease control with conventional topical therapies [14]. Multiple forms of phototherapy are beneficial for disease and symptom control, including UVB or UVA1 types. However, phototherapy is not widely used; the greatest barrier to its use is the need for frequent trips to the medical provider of this form of treatment (two or three sessions a week over 2–3 months).

Systemic immunomodulatory agents are indicated and recommended for patients in whom optimised topical regimens using emollients, topical anti-inflammatory therapy, adjunctive methods and/or phototherapy do not adequately control the signs and symptoms of disease, or when quality of life is substantially impacted [14–16]. Cyclosporin, an immunosuppressant of T cells and interleukin (IL)-2 production, is the only systemic oral medication with marketing authorisation in France for the treatment of adult patients with severe AD.

Other systemic agents, such as methotrexate, azathioprine and mycophenolate mofetil, are not approved for this indication in France, while the 9-*cis*-retinoic acid alitretinoin is only indicated for severe chronic hand eczema [17].

A recent addition to the therapeutic armamentarium for AD is the biological agent dupilumab, which blocks IL-4/IL-13 signalling and thereby inhibits receptor signalling downstream of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway [18, 19]. In France, dupilumab is positioned by the payers as a second-line treatment option (after ciclosporin) and is administered by subcutaneous injection every 15 days to patients with moderate-to-severe AD. Dupilumab can be used in children aged over 12 years whose disease is not adequately controlled with topical therapies or adult patients whose disease is not adequately controlled with ciclosporin or in whom ciclosporin is not advisable (because of contraindications or poor tolerance) [20].

WHAT IS THE COURSE OF THE DISEASE DURING TREATMENT?

In general, the response to topical corticosteroids is good, with a rapid improvement in pruritus and eczema lesions. Improvement is achieved when the treatment is applied for a long enough period of time and in a sufficient quantity for the skin surface to be treated, for example, using the method of the adult fingertip unit (i.e. an amount from the distal interphalangeal joint to the fingertip, or approximately 0.5 g, applied over an area equal to two adult palms). No universal standard exists for the quantity of application, but for maintenance treatment, no more than 60 g of higher-potency agents is recommended per month (i.e. two tubes of topical corticosteroids). Cutaneous adverse effects of topical corticosteroids include purpura, telangiectasia, striae, focal hypertrichosis and acneiform or rosacea-like eruptions on the face. Of greatest concern is skin atrophy, but its incidence during short-term use is generally low. Many of these adverse effects will resolve after treatment discontinuation [12].

While topical calcineurin inhibitors can be prescribed both to reduce topical corticosteroid use and to prevent relapse, their use may be limited by the most common adverse effects seen with these agents—local reactions such as stinging and burning. In my opinion, it is important to avoid applying topical calcineurin inhibitors to acute lesions with a severely impaired skin barrier. These adverse effects tend to lessen after several applications or when combined with periods of topical steroid use [21]. To avoid premature treatment discontinuation, patients should be made aware of these adverse effects and how they can be controlled.

Ciclosporin is particularly useful in patients with severe AD in whom conventional therapy has failed. This compound offers rapid relief from both pruritus and atopic lesions, with a significant decrease in disease activity within 2–6 weeks of treatment initiation [22]. However, long-term use is not recommended because of the risks of nephrotoxicity and hypertension, and continued use of ciclosporin should not exceed 2 years without nephrological monitoring. As a result of its immunosuppressive action, there is also a risk of infection with ciclosporin and patients should be monitored. Patients must also be aware of other potential adverse effects, such as headaches and hypertrichosis.

A newcomer to the field, dupilumab can significantly improve clinical outcomes and quality of life in patients with moderate-to-severe AD. This medication can be administered over a long period of time, with no maximum recommended duration of treatment. The safety profile of dupilumab is superior to that of conventional immunosuppressive agents. Conjunctivitis is the most relevant adverse effect, requiring monitoring and accurate care to avoid premature treatment discontinuation. The impact of dupilumab (an immunomodulatory agent) on infection rates has to be checked, although no concerns were raised in clinical trials [23, 24] or in a recent pooled analysis from seven trials showing that dupilumab is associated with reduced risk of serious/severe infections and non-herpetic skin infections and does not increase overall infection rates versus placebo [25].

OF THE THERAPIES CURRENTLY BEING DEVELOPED, WHICH DO YOU FIND PARTICULARLY PROMISING FOR IMPROVING PATIENT CARE?

As monotherapy or in combination with topical corticosteroids, dupilumab has greatly improved the clinical outcomes and quality of life in patients with moderate-to-severe AD and, as such, constitutes a real breakthrough in the management of this disease. New biological agents are being developed that target the underlying immunological pathophysiology of the disease [18, 19]. Several drugs directly target IL-13, including tralokinumab [26, 27] and lebrikizumab [28], while nemolizumab targets IL-31 and is mainly effective for the treatment of pruritus [29]. Another promising class of medications act by inhibiting JAK1, JAK2 and JAK3, thereby blocking cytokine-mediated signalling via the JAK-STAT pathway, which plays an important role in immunoregulation and normal cell growth. This class includes baricitinib (anti-JAK1/2), upadacitinib (anti-JAK1) and abrocitinib (anti-JAK2), all of which are promising oral treatments for various dermatological conditions including AD [30–32]. We are certainly at the dawn of a therapeutic revolution in the field!

WHAT DO YOU EXPECT FOR THE MANAGEMENT OF PATIENTS WITH AD IN THE FUTURE?

The management of patients with AD must be improved. In France, patients consult their general practitioner (GP) for mild AD and see a specialist for mild-to-moderate AD. The medications suited to the treatment of severe cases can only be initiated in the hospital. However, there are clearly too many patients who fail to receive the best treatment for their condition [33]. The first challenge is to educate GPs and raise awareness that more effective treatments have recently become available for the

management of AD, targeting patients with AD and the general population via organisations, such as ResoEczema and patients' associations. Encouragingly, over the last 18 months, we have noted an increasing number of patients with moderate-to-severe AD being referred to our hospital. This observation suggests that more and more patients are being appropriately guided by healthcare professionals to benefit from the best treatments available.

In France, as in many other countries, rules apply to prescription of medications. For example, for patients with moderate-to-severe AD, the payers positioned dupilumab for the adults as a second-line medication that can only be prescribed by hospital practitioners in patients with treatment failure, contraindication or intolerance to ciclosporin. If we anticipate comparable rules for the prescription of the next generation of therapies for AD, it is important that patients are appropriately prescribed first-line treatment agents, so they may subsequently benefit from innovative second-line options as they become available.

Today, we are at the dawn of a therapeutic revolution for AD with the emergence of various treatment options that will potentially enable better and longer-lasting symptom control and enhance the quality of life of patients and their families. The primary duty of healthcare professionals and treatment networks is to ensure that all patients are able to benefit from these innovative treatments by receiving the treatment that is best suited to their disease.

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